
POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY
Assessment of the Appropriate Net Container Content for Injectable Drug and Biological Products

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PURPOSE

This MAPP establishes procedures for the assessment and documentation of the net container content(s)¹ for injectable drug products filled into vials² including drug products that require constitution/reconstitution submitted in new drug applications (NDAs), biologics license applications (BLAs) seeking licensure under 351(a) of the Public Health Service Act (PHS Act), and supplements to these applications that propose new strengths. This MAPP applies to drug³ products in single-dose and multiple-dose vials including drug products approved for dosing regimens with fixed doses and drug products approved for dosing regimens with doses based on body weight or body surface area.⁴ This MAPP also establishes what information regarding the net container

¹ In this MAPP, “net container content” is synonymous with “labeled vial fill size” as described in the FDA guidance for industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015), and refers to net quantity of contents as described in 21 CFR 201.51. The net container content shall appear as a distinct item on the label (21 CFR 201.51(d)). For injectable drug products that are marketed as: 1) liquids – the net container content will be expressed as a measure of volume (e.g., milliliter (mL)); 2) solids – the net container content will be expressed as a measure of weight (e.g., milligram (mg)) (see 21 CFR 201.51(a)).

² The term “vial” used throughout this MAPP refers to both vial and ampule package types.

³ The term “drug” used throughout this MAPP refers to drugs, including biological drug products that are in scope of the MAPP.

⁴ For the definition of multiple-dose (i.e., multi-dose) and single-dose, see FDA guidance for industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018), and the United States Pharmacopeia (USP) General Chapter <659> *Packaging and Storage Requirements, Injection Packaging Systems*.

content(s) for injectable drug products filled into vials should be communicated to sponsors⁵ during product development.

The policies and practices established by this document are intended to standardize the Office of Pharmaceutical Quality (OPQ) assessment of information contained in the electronic Common Technical Document (eCTD) section 3.2.P.2., Pharmaceutical Development.

The principles outlined in this MAPP may also apply to different injection packaging types (e.g., prefilled syringe package systems and intravenous infusion bags) and abbreviated new drug applications (ANDAs) in which a suitability petition for a different drug product strength has been approved.⁶

BACKGROUND

This MAPP conveys information related to OPQ's implementation of the final guidance for industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015). The guidance provides recommendations to industry on two topics: 1) allowable excess volumes during manufacturing of injectable drug products filled into vials, and 2) appropriate drug product net container content sizes (i.e., labeled vial fill sizes) for injectable drug products.

As a companion to this MAPP, MAPP 5019.1 *Allowable Excess Volume/Content in Injectable Drug and Biological Products* provides information on excess content of injectable drug products filled into vials. This MAPP outlines considerations for FDA staff reviewing relevant applications and supplements to ensure sponsors develop the appropriate drug product net container content(s). The proper net container content is important for proper dosing of the patient, to minimize medication errors, to avoid drug product contamination, and to limit drug product waste.

Misuse of injectable drug products filled into vials and other packaging types, including unsafe handling and injection techniques, has led to drug product contamination and an increased risk of bloodborne illness transmission between patients. A factor that can contribute to unsafe handling and injection practices by patients and health care providers is inappropriate net container content sizes resulting in:

- An excess of drug product that could be used as a partial dose or pooled to produce a second dose; and/or

⁵ In this MAPP, "sponsors" include applicants who are pursuing approval of an application or a new package size postapproval.

⁶ For ANDAs, unless a suitability petition for a different drug product strength has been approved, an ANDA is required to select from the approved product strengths of the reference listed drug (RLD). See 21 CFR 314.94. When reviewing a suitability petition in accordance with MAPP 5240.5 Rev 2 *ANDA Suitability Petitions* (October 2020), a labeled net container content change request for a parenteral drug product will include considerations set forth in this MAPP.

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- The need to use multiple vials to dose a single patient, which can lead to an increased risk of contamination due to inappropriate aseptic technique when combining material from different vials.

There are unique considerations for drug products dosed by body weight or body surface area. Marketing only one single-dose drug product net container content to cover all possible doses may necessitate the need to use multiple vials for some patients and may result in medication errors. In addition, there can be a significant amount of leftover drug product after administration. Leftover drug after administration may encourage pooling of the remaining contents to make additional doses. This, in turn, may lead to adverse events because the practice of puncturing single-dose vials multiple times and pooling preservative-free drug product may lead to contamination of the pooled drug product, particularly if unsafe handling techniques are used. For example, if the patient dose ranges from 225 mg to 510 mg and the vial net container content is 100 mg, multiple 100 mg vials would need to be pooled for administration and a significant amount of leftover drug product could remain in the last vial depending on the patient dose. In this example, for the lowest 225 mg dose, a practitioner would need to pool the contents of three 100 mg vials, and after withdrawal of the 225 mg dose, the unused drug product remaining in the third vial would be approximately 75 mg. This substantial amount of unused drug product encourages pooling of leftover contents to be used as additional doses.

POLICY

- The Office of New Drug Products (ONDP) or Office of Biotechnology Products (OBP) quality assessor⁷ will inform an investigational new drug (IND) sponsor as early as possible in the product development process that the proposed drug product net container content(s) should be appropriate for the intended use and dosing.
- OPQ will request a justification from the sponsor for the drug product net container content(s), if not provided, no later than the end of phase 2 to ensure the sponsor has sufficient time to generate adequate stability data in the event a change in the drug product net container content is needed to support the submission of the NDA or BLA.
- If needed, OPQ may consult the Office of New Drugs to provide input to the quality assessor related to drug product net container content(s) based on available clinical information derived from clinical trial data, published literature, or other sources of clinical data.

⁷ In this document, we use the term *assessment* instead of the term *review*. Assessment means the process of both evaluating and analyzing submitted data and information to determine whether the application or supplement meets the requirements for approval and documenting that determination.

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- If needed, OPQ may consult the Office of Surveillance and Epidemiology (OSE)/Division of Medication Error Prevention and Analysis (DMEPA) to provide recommendations related to proposed drug product net container content(s) from a medication error perspective.

RESPONSIBILITIES

ONDP, OBP, OLDP,⁸ or OPMA⁹ Quality Assessor

For INDs, NDAs, BLAs, and their supplements, determines the appropriateness of the net container content(s) for an injectable drug product.

OND Clinical Reviewer

When requested:

- Verifies the expected dosing range.
- Assesses clinical risk for overdosing (e.g., increased toxicity) or underdosing (e.g., reduced efficacy) because of the drug product net container content(s). This may include an assessment of clinical information from dose-finding clinical trials and consideration of exposure-response and dose-response relationships for safety and efficacy.

OSE/DMEPA 1 or DMEPA 2 Safety Evaluator

When consulted:

- Provides recommendations related to proposed drug product net container content(s). Their recommendations may specifically address whether the drug product net container content(s) proposed in the application or supplement is appropriate from a medication error perspective.

⁸ In the event that there is a supplemental change for new net container content(s) for an approved NDA, the Office of Lifecycle Drug Products (OLDP) quality assessor should confirm that adequate justification is provided in the supplement.

⁹ Microbiological information submitted in an NDA or BLA to support the labeled in-use period should be evaluated by the quality assessor in Office of Pharmaceutical Manufacturing Assessment (OPMA).

PROCEDURES**1. The ONDP or OBP quality assessor will:**

- a. Communicate to the sponsor as early as possible during development that the drug product net container content(s) should be appropriate for the intended use and dosing of the drug product.
- b. For dosing based on body weight or body surface area in multiple containers of varying net container contents, request a justification from the sponsor for the proposed drug product net container content(s) no later than the end of phase 2, if not provided. The justification should include whether the development of a single- or multiple-dose vial is needed to cover the typical adult dose range in a manner that minimizes dosing errors and limits the amount of leftover drug product in the vial after administration.
- c. For a fixed dose drug product in a single-dose container, request a justification from the sponsor for the proposed drug product net container content(s) if there is significant¹⁰ drug product left in the single-dose vial following withdrawal of a fixed dose, or more than one vial is required for administration of a dose. If such a justification is needed, the request should be communicated to the sponsor no later than the end of phase 2.
- d. For a drug product provided in a multiple-dose container, request a justification from the sponsor for the proposed drug product net container content(s) no later than the end of phase 2. The justification should consider the dose of the drug product, the net content in excess of 30 mL,¹¹ the number of times the stopper could be punctured and still maintain its integrity, and the amount of drug product that could reasonably be used in 28 days.¹²

¹⁰ While it is not possible to specify a quantitative volume of remaining drug product that would generally be considered significant, volumes remaining that could provide a second dose, or would encourage pooling for a second dose, would be considered significant.

¹¹ Per USP General Chapter <659> *Packaging and Storage Requirements, Injection Packaging Systems*, multiple-dose vials have a maximum container volume sufficient to permit the withdrawal of not more than a total of 30 mL, unless otherwise specified in an applicable USP drug product monograph. Exceeding the 30 mL multiple dose vial limit may be justified if the recommended dose of the drug product packaged in a multiple dose vial is large, making the 30 mL limit impractical.

¹² The beyond-use date for an opened or entered (e.g., needle-punctured) multiple-dose container is 28 days, unless otherwise specified by the manufacturer on the label. See

<https://www.jointcommission.org/standards/standard-faqs/nursing-care-center/medication-management-mm/000001529/>

- e. Consult with the OND clinical reviewer and the OSE/DMEPA safety evaluator to identify potential safety or efficacy concerns with the proposed drug product net container content(s), if deemed necessary.
 - f. Communicate to the sponsor any identified issues with the proposed net container content(s).
 - g. Coordinate with the relevant review disciplines and, in the absence of adequate justification, issue an information request letter or complete response letter to the sponsor for the identified net container content issue(s). Options for proposed changes include adjustment of the drug product net container content by changing the fill volume, changing the concentration of the active ingredient in the formulation, or adding additional options for net container content(s) as appropriate.
 - h. Summarize drug product net container content issues and document this information in the appropriate product quality assessment template.
- 2. For multiple-dose vials, the ONDP, OBP, or OPMA quality assessor will:**
- a. Evaluate for appropriateness when the net content of drug product is greater than 30 mL.
 - b. Confirm that appropriate chemical and microbiological information has been submitted to support the labeled in-use period. If no in-use period is specified in the labeling, the data should support an in-use period of 28 days after first entry.
 - c. Ensure that adequate justification is provided for the proposed drug product net container content(s). It should include the proposed dosing range of the drug product, the number of times a stopper can be punctured and still maintain its integrity, and the amount of drug product that can reasonably be used in 28 days.
- 3. For drug products administered as a fixed dose, the ONDP or OBP quality assessor will:**

Confirm that the amount of drug product in a single-dose vial contains only a single dose by requesting a justification from the sponsor for the proposed drug product net container content(s) when:

- There is significant drug product left in the vial following withdrawal of a fixed dose from a single-dose vial.
- More than one vial is required for administration of the dose.

4. For dosing based on body weight or body surface area, the ONDP or OBP quality assessor will:

- a. Evaluate the proposed net container content(s) and justification to ensure that dosing flexibility is provided across the intended U.S. patient population in the application or supplement to avoid excessive pooling of multiple vials and to minimize leftover drug product in the vial.
- b. Consult the OND clinical reviewer, if necessary, to confirm whether the sponsor's dosing range analysis is appropriate.

REFERENCES

1. FDA draft guidance for review staff and industry *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications* (September 2018, rev. 1)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf>
2. Guidance for industry M2 eCTD: Electronic Common Technical Document Specification (April 2003); section 3.2.P.2., Pharmaceutical Development
3. FDA guidance for industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015)
4. FDA guidance for industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018)
5. United States Pharmacopeia (USP) General Chapter <659> *Packaging and Storage Requirements, Injection Packaging Systems*
6. MAPP 5019.1 *Allowable Excess Volume/Content in Injectable Drug and Biological Products* (January 28, 2022)
7. MAPP 5240.5 Rev 2 *ANDA Suitability Petitions* (October 9, 2020)

EFFECTIVE DATE

This MAPP is effective on June 6, 2022.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
6/6/2022	N/A	Initial version